



Substrate and reagent control of diastereoselectivity in transition metal mediated processes :
development of a catalytic photopromoted Pauson-Khand reaction
by Brian L Pagenkopf

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in
Chemistry
Montana State University
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Abstract:

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Brian L. Pagenkopf

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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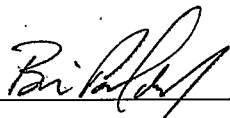
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For the Believers

Satisfaction lies in the effort not in the attainment. Full effort is full victory.

Mahatma Gandhi

Character is higher than intellect. A great soul will be strong to live, as well as to think.

Ralph Waldo Emerson

One science only will one genius fit: So vast is art, so narrow human wit.

Alexander Pope

There is no great genius without a tincture of madness.

Seneca

Don't be afraid to challenge the pros, even in their own backyard. Just as important, never neglect details, even to the point of being a pest.

Colin Powell

There is great ability in knowing how to conceal one's ability.

Francis, Duc de La Rochefoucauld

As for *work*, we haven't any of any consequence.

Henry David Thoreau

Not by years but by disposition is wisdom acquired.

Plautus

Four to six weeks in the lab can save you an hour in the library.

G. C. Quaderer, Dow Chemical

In matters of style, swim with the current; in matters of principle, stand like a rock.

Thomas Jefferson

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Abstract

Several of the factors that influence substrate based control of diastereoselection in $\text{Cp}_2\text{Zr(II)}$ mediated enyne cyclizations have been illuminated by examination of an extensive series of substituted enynes. An eminently practical, catalytic, photopromoted Pauson-Khand reaction that proceeds under mild reaction conditions (50 - 55 °C) under 1 atm of CO was developed. The photopromoted Pauson-Khand reaction is compatible with substrates bearing of a wide variety of functional groups and substitution patterns. In some instances, substrate modification resulted in improved yields and increased diastereoselection. Studies directed toward the synthesis of carbacyclin resulted in a short enantiocontrolled synthesis of the epi-carbacyclin core. The key steps of this synthesis were an Evans syn-aldol condensation and ring closure by the catalytic photopromoted Pauson-Khand reaction.

1. Introduction

In recent years, the development of new transition metal mediated processes has become one of the most active and exciting areas of research in synthetic chemistry. The power of metal mediated processes often lies in their ability to confer a high degree of molecular complexity to inexpensive and structurally simple starting materials with relatively little cost or effort. The direct formation of bicyclic metallocyclopentenes from simple enynes by group IV metallocene reagents illustrates the synthetic potential of this class of reactions. Because the intermediate metallocyclopentenes can be further functionalized by a variety of electrophiles, an array of cyclic products is available from the same acyclic precursor.

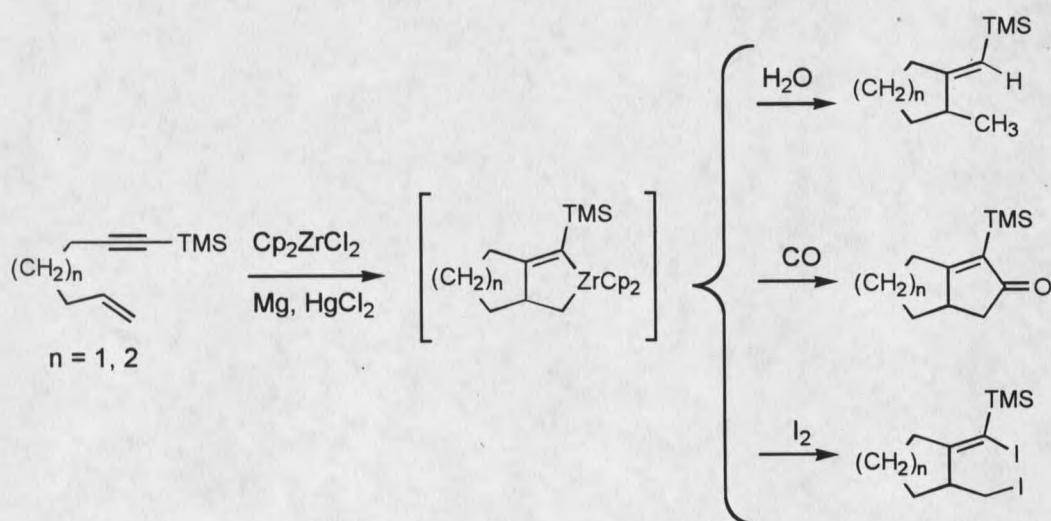
In order to further understand factors that contribute to substrate control of diastereoselectivity in $\text{Cp}_2\text{Zr(II)}$ mediated enyne cyclizations, a diverse series of substituted enynes has been synthesized and subsequently studied in cyclization reactions. The results of these experiments led to the evolution of several synthetic strategies directed toward the synthesis of carbacyclin. The key ring forming step of these synthetic endeavors focused on the use of a $\text{Cp}_2\text{Zr(II)}$ mediated enyne cyclization and tandem carbonylation sequence. The search for an improved

cyclization protocol to effect this transformation has led to the development of a novel, catalytic photopromoted Pauson-Khand reaction.

2. Background

2.1 Early Zirconium(II) Chemistry

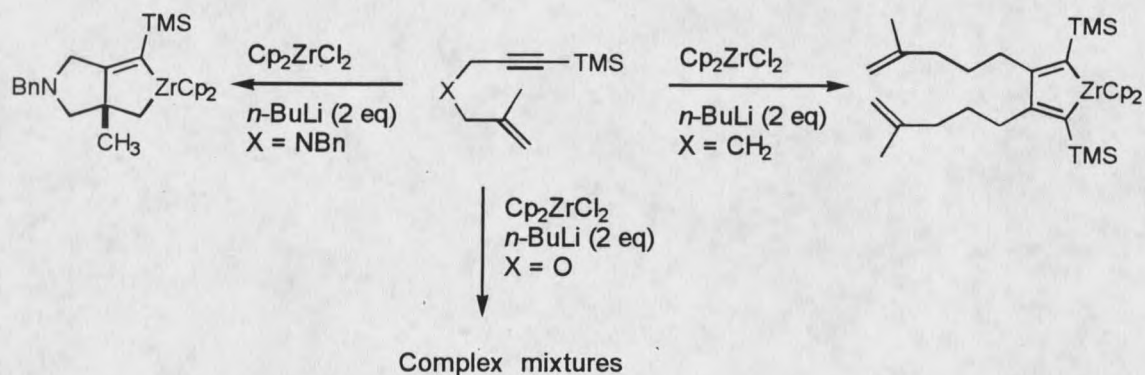
In 1985, Negishi reported that a zirconocene equivalent, i.e. "Cp₂Zr", generated by the treatment of Cp₂ZrCl₂ with Mg and HgCl₂ was effective for converting various non-terminal enynes to zirconocyclopentenes (**Scheme 1**).¹ The chemistry of these metallocycles proved to be diverse and powerful, in that functionalized carbocycles could be obtained from simple acyclic precursors. The intermediate zirconocycles could be protonated to yield the methyldiene substituted cyclopentanes, treated with CO (1 atm), to provide the corresponding α -silyl



Scheme 1

cyclopentenones, or treated with I_2 , to give the 1-vinyl-4-alkyl diiodo derivatives, all in moderate yields. Negishi later reported that treatment of Cp_2ZrCl_2 with two equivalents of $n-BuLi$ at low temperatures offered an easy and economical method for the *in situ* preparation of a zirconocene equivalent.² This disclosure resulted in the rapid acceptance of "zirconocene" as a useful synthetic reagent. The flourish of research since Negishi's initial disclosure has resulted in many contributions leading to the rich and interesting chemistry of zirconium(II) species.^{2b,3}

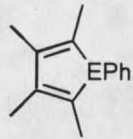
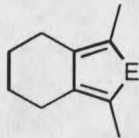
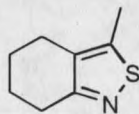
Some heteroatom linkages were found not only to be tolerant of the reaction conditions, but increased the reactivity of 1- or 2-substituted alkenynes (**Scheme 2**).⁴ Substituted alkenes with a carbogenic tether failed to react in the usual manner, but instead dimerized to give zirconocyclopentadienes in good yield. The heteroatom contraction offered by a benzylamine linkage resulted in the expected zirconocyclopentene product even with substituted alkenes. Oxygen tethers resulted in complex product mixtures,⁵ although with dienes (*vide infra*, section 2.3 (Chapter 2, subsection 3)) this reactivity has been attenuated to become a route to allylic- and propargyliczirconocene derivatives.⁶



Scheme 2

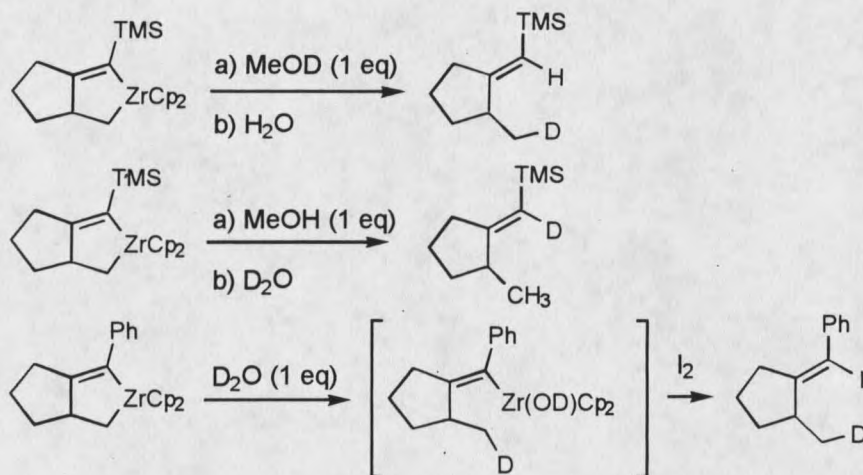
Fagan and Nugent later showed that zirconocyclopentadienes effectively transmetallated with main group electrophiles to afford main group heterocycles (Table 1).⁷ Substrates 1 and 2 were easily prepared from 2-butyne or 2,8-decadiyne. Entry 3 was prepared by the addition of 1-cyano-5-heptyne to a solution of $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$ reduced *in situ* in the presence of bis(trimethylsilyl)acetylene. These preparations represented a superior route to these main group heterocycles.

Table 1. Main Group Heterocycles by Metallacycle Transfer from Zirconium.

Electrophile	Product	Element, (Yield)
1. PhECl ₂		E = P, (85%) As, (76%) Sb, (78%) Bi, (70%)
2. E ₂ Cl ₂		E = S, (55%) Se, (50%)
3. S ₂ Cl ₂		(65%) ^a

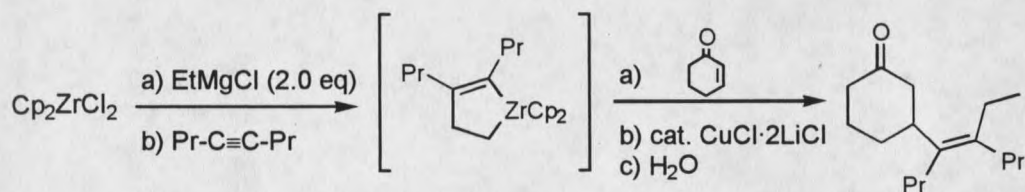
^a Based on recovered starting material.

Although both the sp² and sp³ carbons bound to zirconium effectively transmetallate to main group electrophiles, they have sufficiently different nucleophilicity to allow selective mono functionalization. The sp³ carbon reacts readily with one equivalent of electrophile, whereas initial reaction at the sp² carbon is virtually unknown. Deuteration of a zirconocyclopentene with deuterio-methanol (1 eq) followed by aqueous work-up afforded the cyclopentane in excellent yield with deuterium incorporation solely on the methyl group. Treatment of the zirconocycle with methanol (1 eq) followed by an acidic deuterium oxide quench provided the cyclopentane with deuterium incorporation solely at the vinylic position.⁸ Other electrophiles, such as iodine also followed the same reactivity pattern (**Scheme 3**).⁹



Scheme 3

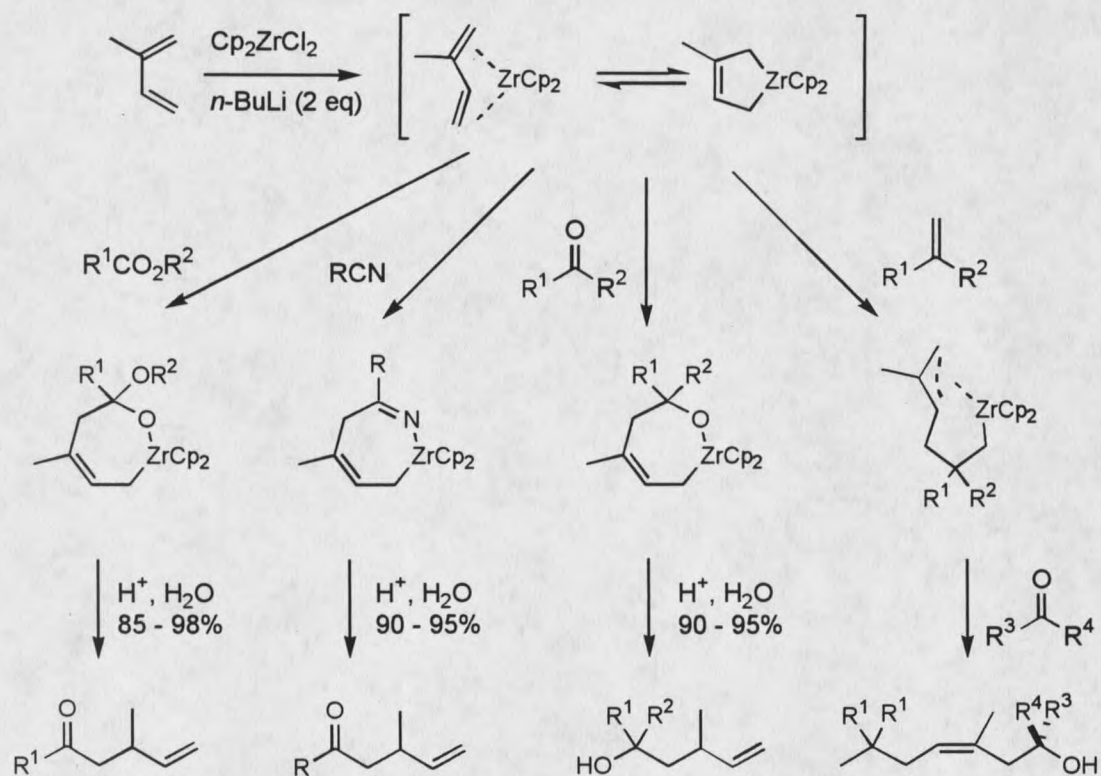
Lipshutz has shown that catalytic Cu(I) converted the zirconium bound sp^2 carbon of a zirconocyclopentene into a highly reactive cuprate intermediate that rapidly undergoes 1,4-addition to α,β -unsaturated enones (Scheme 4).¹⁰



Scheme 4

Zirconocyclopent-3-enes, derived from the reaction of Cp_2ZrCl_2 reduced *in situ* in the presence of *conjugated* dienes (e.g. isoprene), demonstrate diverse reactivity and high nucleophilicity (Scheme 5).^{4b} They may be viewed as allylzirconocene derivatives which react with polar or non-polar π -systems. It is

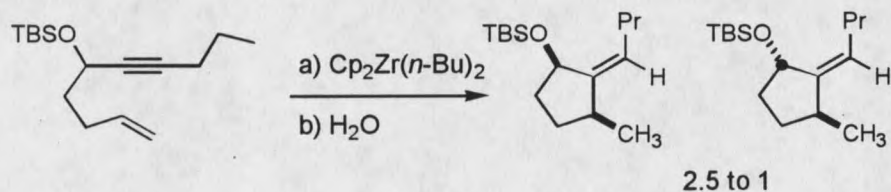
interesting to note that polar π -systems reacted adjacent to the methyl group while nonpolar π -systems reacted with the less hindered carbon.



Scheme 5

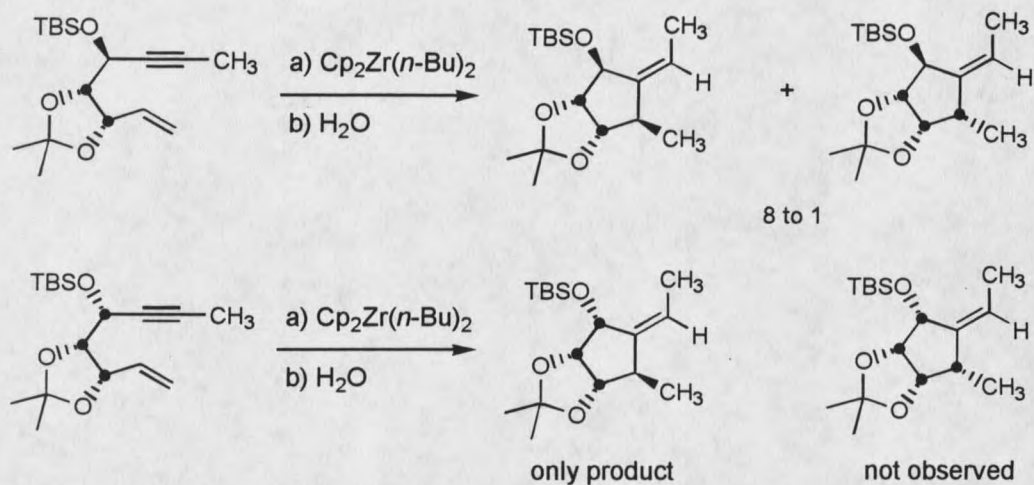
2.2 Diastereoselectivity in Zirconium(II) Enyne Cyclizations

The elucidation of processes that control the relative and absolute stereogenesis of chemical transformations is critical for mechanistic interpretations and planning synthetic strategies. In 1989, RajanBabu and Nugent described the first example of substrate control in stereoselective “zirconocene” mediated enyne cyclizations.¹¹ Cyclization of 6-siloxy-non-9-en-4-yne afforded *cis*- and *trans*-alkylidene-cyclopentanes in a 2.5 to 1 ratio in 94% overall yield (**Scheme 6**).



Scheme 6

Armed with the knowledge that “zirconocene” mediated enyne cyclizations occurred with moderate substrate derived stereocontrol, they prepared an enantiomerically pure $4\beta,5,6\alpha$ -trisubstituted enyne that cyclized to give diastereomeric alkylidines in an 8 to 1 ratio in 71% overall yield (**Scheme 7**). The epimeric trisubstituted enyne provided only one diastereomeric product.



Scheme 7

No rational analysis of the influences of ring substitution on stereoselection of zirconium(II) mediated enyne cyclizations was undertaken until Livinghouse and Lund, in a preliminary communication, examined a series of singly substituted enynes.¹² Excellent levels of diastereoselection were observed in that each example gave only a single diastereomeric product (**Table 2**). The intermediate zirconocyclopentenes formed from the zirconium(II) enyne cyclizations can equilibrate to the thermodynamically most stable product, although rationalization of the stereochemical outcome has also been based on kinetic arguments.¹³ Further exploration of stereoselection in zirconium(II) mediated cyclizations of monosubstituted enynes constitutes part of this thesis.¹⁴

Table 2. Diastereoselective Cyclizations with $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$

Entry	Substrate	Product	Yield ^a
1	$\text{R}^1 = \text{TBS}, \text{R}^2 = \text{TMS}$		79%
2	$\text{R}^1 = \text{TBS}, \text{R}^2 = \text{SCH}_3$		53%
3	$\text{R}^1 = \text{Li}, \text{R}^2 = \text{SCH}_3$	$\text{R}^1 = \text{H}, \text{R}^2 = \text{SCH}_3$	70%
4	$\text{R} = \text{TBS}$		68%
5	$\text{R} = \text{Li}$	$\text{R} = \text{H}$	70%
6	$\text{R} = \text{TBS}$		78%
7	$\text{R} = \text{Li}$	$\text{R} = \text{H}$	81%

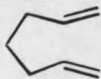
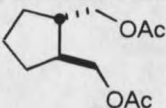
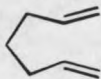

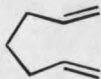

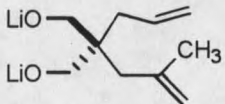
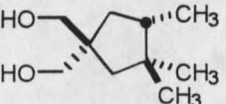
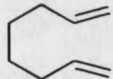
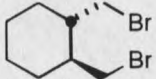
^a Isolated yield. No other diastereomers observed.

2.3 Zirconium(II) Diene Cyclizations

The zirconium(II) carbometallation reactions of non-conjugated dienes remained unexplored until 1989, when Nugent and Taber showed that dienes were efficient substrates for reductive bicyclization.¹⁵ The intermediate zirconium metallacyclopentanes can be trapped with a variety of electrophiles such as Br_2 , main group electrophiles (including BCl_3),¹⁶ and CO , usually in excellent yield

(Table 3). Note in entry three the major diastereomer was the *trans*-bicyclo[3.3.0]octane.

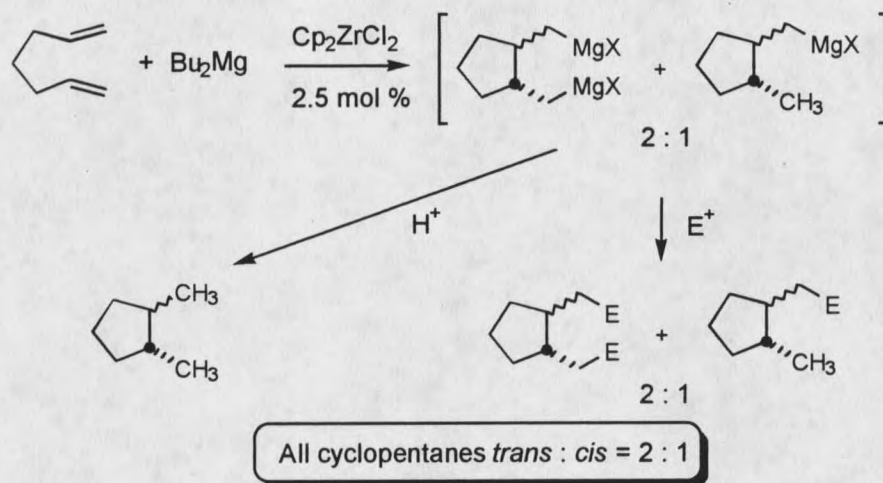
Table 3. Cyclization of Dienes with $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$ and varied Electrophilic Capture

Entry	Diene	Electrophile	Product	Yield ^a
1		O_2		80% ^b
2		Ph_2SnCl_2		67%
3		CO		53% ^c
4		H^+		73%
5		Br_2		63%

^a Isolated yield of major diastereomer (shown). For entries 1 and 2 the presence of another diastereomer was not disclosed. ^b The crude product was treated with acetic anhydride / pyridine prior to chromatography. ^c 14 to 1 diastereomer ratio in 53% combined yield.

The use of Cp^*ZrCl_3 (Cp^* = pentamethylcyclopentadienyl anion) instead of Cp_2ZrCl_2 reversed the usual trend of *trans*-cyclopentanes (or *trans*-bicyclo[3.3.0]octanes) and gave *cis*-substituted cyclopentanes (or *cis*-bicyclo[3.3.0]octanes) as the major diastereomer. The high cost of Cp^* and the need for stoichiometric quantities of Cp^*ZrCl_3 has precluded the adaptation of this reagent in synthesis. However, the discovery that Cp_2ZrCl_2 could be used

catalytically in the formation of cyclic carbometallated products from non-conjugated dienes was an exciting development.¹⁷ With only a catalytic amount of zirconium reagent required, even costly homochiral metallocene reagents could be used.¹⁸ Efficient conversion required that Bu_2Mg be used as the stoichiometric reagent, although only 60% of the products are dimetallated (**Scheme 8**).¹⁹ This shortcoming limits further functionalization of the intermediate cyclopentanes and has hindered its adoption as a new synthetic tool.

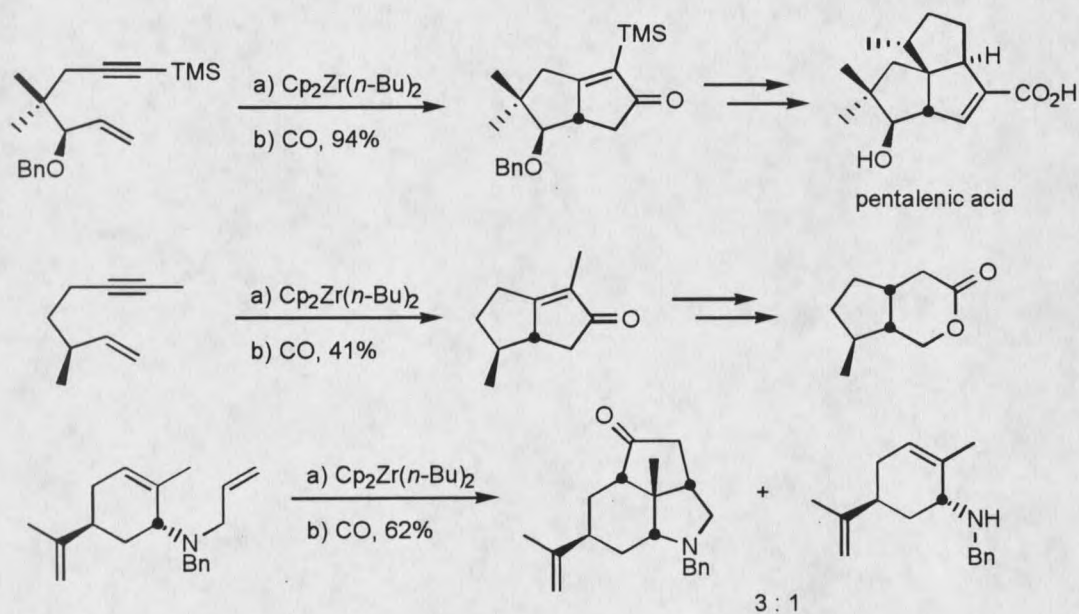


Scheme 8

2.4 Cyclopentenones

The carbonylation of zirconocyclopentenes (**Scheme 1**) and zirconocyclopentanes (**Table 3**) is perhaps the most powerful reaction in the arsenal of zirconocene chemistry. In the reaction, an acyclic carbogenic enyne is

transformed into a functionalized bicyclic enone which can be manipulated into more elaborate structures. Negishi's synthesis of pentalenic acid²⁰ and iridomyrmecin²¹ and Mori's formal synthesis of dendrobine^{22b} all demonstrate the utility of this powerful method (**Scheme 9**). In the last example, the substrate suffers from fragmentation of the nitrogen and propenyl moiety (c.f., **Scheme 2**).

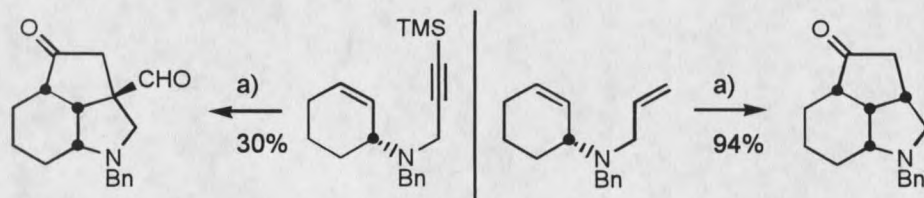


Scheme 9

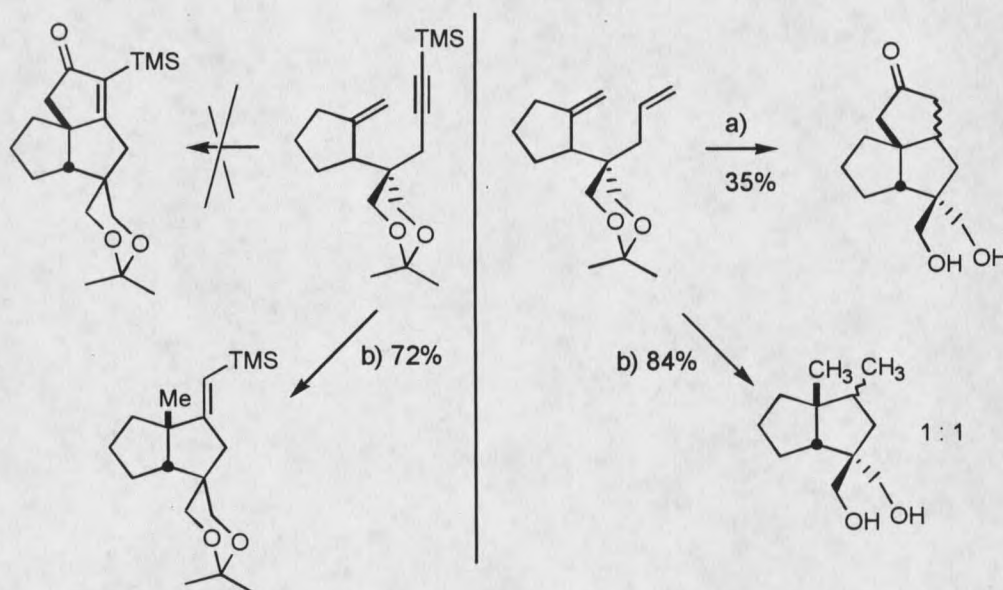
Yields of ketones obtained from zirconocycles are consistently better when derived from dienes compared to their enyne counterparts (**Scheme 10**). In the first example, the diene underwent cyclization and carbonylation in excellent yield, whereas the enyne was a poor substrate.²² The enyne in example one uniquely incorporated two equivalents of CO. In the second example, the corresponding enyne failed to incorporate any CO at all.²³ It is important to note that when the

intermediate zirconocyclopentene was quenched with water, the cyclized product was obtained in high yield. Zirconocyclopentanes have been converted into cyclopentanones by insertion of an isonitrile followed by hydrolysis of the resulting imide.²⁴

Example 1



Example 2



Reagents: (a) i. $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$; ii. CO; iii. H_3O^+ ; (b) i. $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$; ii. 10% HCl

Scheme 10

Several other highly successful methods exist for preparing bicyclic cyclopentenone derivatives. The elegant method of Buchwald used a catalytic amount of $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$ and a stoichiometric amount of isonitrile to convert enyne into bicyclopentenones (in 40-80% yield).²⁵ The key to the successful implementation of this methodology required the use trialkylsilylnitriles, which are in equilibrium with a small amount of trialkylsilylisonitrile; this essentially reduces the concentration of free isonitrile in solution to almost zero. The methodology worked with substrates that fail with titanocene or zirconocene, including enynes containing sensitive functional groups (e.g., esters, oxygen tethers). The method as initially described may not see widespread adoption because the extremely air and moisture sensitive nature of the catalyst necessitates that the reactions be performed in a dry box. However, the *in situ* generation of $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$ from air-stable Cp_2TiCl_2 and two equivalents of *n*-BuLi in the presence of PMe_3 appears to provide an easy route to an equally active catalyst.²⁶ The method is perhaps most limited in requiring only non-terminal alkynes. However, since this writing, a communication by Buchwald has appeared that employs the commercially available $\text{Cp}_2\text{Ti}(\text{CO})_2$ in catalytic quantities.²⁷ This methodology worked successfully with a variety of enynes containing sensitive functionality, 1,2-disubstituted alkenes and one example of a primary alkyne. However, the reaction required 2.3 atm of CO. Buchwald

suggested that the two catalyst systems do not go through the same titanacyclopentene intermediate, but offered no explanation.

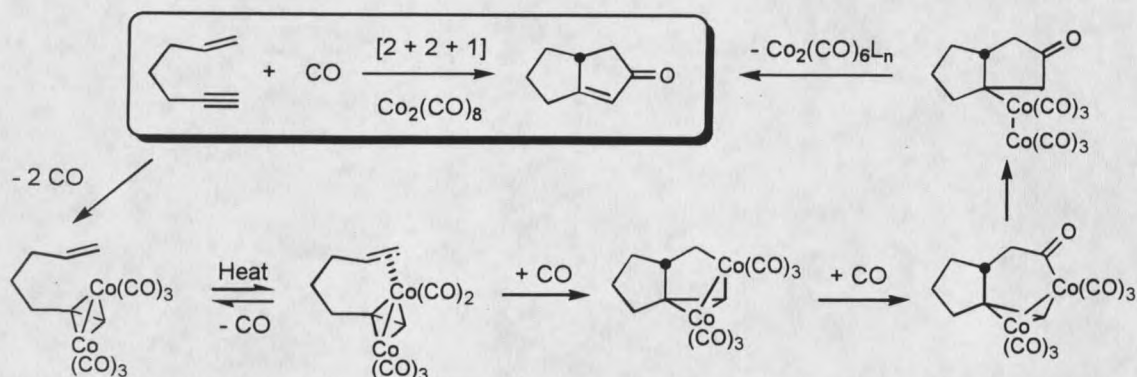
A second communication by Buchwald describing the synthesis of enones employing a nickel catalyst has appeared.²⁸ This catalyst system used a ligand derived from 1,2-diaminocyclohexane. The focus of this work is clearly to develop an asymmetric variation of this reaction.

2.5 The Pauson-Khand Reaction

Perhaps one of the most convergent methods for the synthesis of cyclopentenones is the Pauson-Khand reaction, which represents a formal [2+2+1] cycloaddition involving an alkyne, alkene and carbon monoxide (**Scheme 11**). This subject has been extensively reviewed.²⁹ The Pauson-Khand reaction successfully generates cyclopentenone derivatives by both inter- and intramolecular variations. In a typical procedure, the enyne is mixed with one equivalent of $\text{Co}_2(\text{CO})_8$ and then heated (either at reflux or in a sealed tube) for several hours to days. Common solvents are heptane, toluene and acetonitrile. The synthetic utility of the Pauson-Khand reaction was enhanced when it was disclosed that silica gel, tertiary amine *N*-oxides and DMSO markedly accelerate the reaction.³⁰ The Pauson-Khand reaction works with enynes containing sensitive functionality, including esters,

oxygen tethers and primary alkynes. (The first example of a zirconocene mediated cyclization-carbonylation reaction of a pseudo *terminal* alkyne was recently reported).³¹

The alkyne•Co₂(CO)₆ complexes formed in the initial stages of the reaction are typically air-stable compounds and are readily isolated and characterized. No later intermediates in the mechanistic pathway have yet been identified. The next step requires heat or amine oxides to promote CO disassociation followed by alkene complexation to the vacant coordination site on cobalt. Irreversible alkene insertion then occurs in the rate determining step, also setting the stereochemistry in chiral substrates. Next, migratory CO insertion followed by reductive elimination furnishes the enone as its Co₂(CO)₆ complex. Another reductive elimination affords the final product and regenerates the Co₂(CO)₆L_n metal catalyst. In principle, the thermal Pauson-Khand reaction should be catalytic. Indeed, low levels of catalytic turnover have been observed, but the high temperatures required for CO disassociation probably decompose the transient unbound Co₂(CO)₆L_n catalyst (*vide infra*, section 3.5).²⁹



Scheme 11

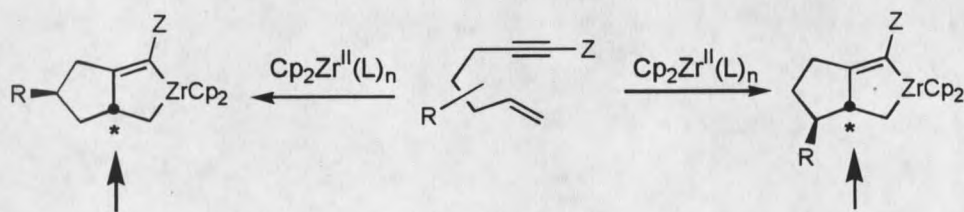
A major disincentive to the large scale use of the classical Pauson-Khand reaction rests in its requirement for stoichiometric quantities of $\text{Co}_2(\text{CO})_8$.³² However, Jeong and collaborators recently reported that selected 1,6-enynes could be converted to the corresponding cyclopentenones in the presence of CO (at 4-5 atm pressure), 3-5 mol % $\text{Co}_2(\text{CO})_8$ and 10-20 mol % $(\text{PhO})_3\text{P}$ at 120 °C.³³ Although highly significant as one of a very limited number of successful accounts involving truly catalytic quantities of $\text{Co}_2(\text{CO})_8$,³⁴ the relatively strenuous conditions of the Jeong procedure may discourage its widespread adoption in many laboratory settings or for use with sensitive substrates. The development of a photo-promoted catalytic Pauson-Khand reaction requiring only 1 atm of CO constitutes part of this thesis.

A variety of other reagents capable of effecting the Pauson-Khand reaction also exist. The tungsten based reagent $\text{W}(\text{CO})_5 \cdot \text{THF}$ has been shown to promote the Pauson-Khand reaction in a batch-catalytic manor, but in only poor to moderate

(ca. 25-65%) yields.³⁵ The Pauson-Khand reaction is also promoted by iron carbonyl complexes under strenuous conditions (2 eq $\text{Fe}(\text{CO})_5$, 135-140 °C, 4-5 atm CO, 21-64 h) and with poor to moderate yields.³⁶ Recently, Sato demonstrated that the $(\eta^2\text{-propenyl})\text{Ti}(\text{O-}i\text{-Pr})_2$ complex could mediate carbonylation of enynes.³⁷ Only two examples were given, both in poor yield. Finally, bicyclic enones are obtained from by treating a 1,6-diyne with catalytic $\text{Rh}(\text{acac})(\text{CO})_2$ in the presence of stoichiometric trialkylsilane under 15 atm of CO.³⁸

3. Results and Discussion

The elucidation of processes that control relative and absolute stereogenesis has become central to the practice of selective organic synthesis. In this context, transformations mediated by transition metals have gained increasing recognition as a powerful means for achieving reaction selectivity. This characteristic is derived, in part, from the ability of transition metals to serve as vehicles for both substrate³⁹ and reagent⁴⁰ based stereocontrol. The intramolecular Pauson-Khand reaction has been utilized quite frequently for the construction of fused 2-cyclopenten-1-ones (*vide supra*, section 2.5). Although numerous studies addressing the diastereoselective nature of this cobalt-centered annulation have appeared, comparatively little has been reported regarding the corresponding $\text{Cp}_2\text{Zr(II)}$ mediated cyclizations.⁴¹ The potential utility of Group IV metal templated cyclizations for the synthesis of bioactive [3,4] fused cyclopentenones warranted



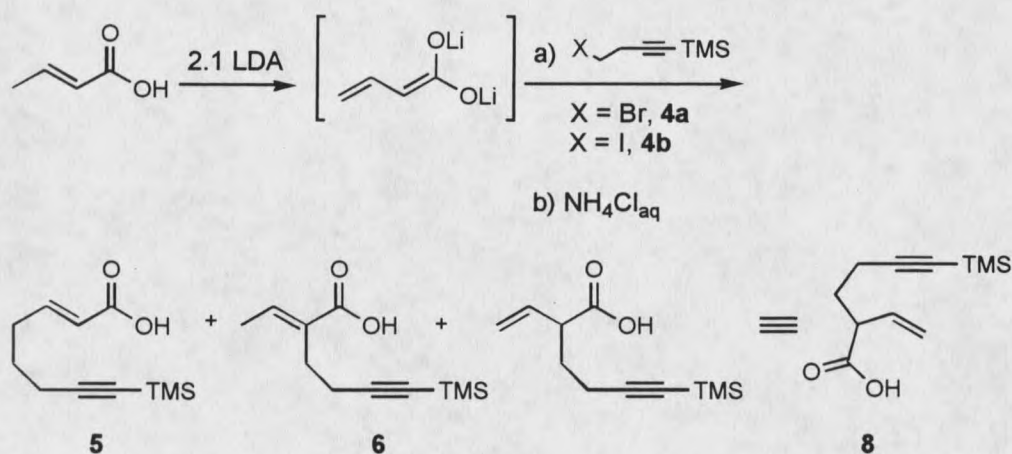
Scheme 12

continuation of the initial investigations of substrate directed stereocontrol in Zr-ene cyclizations (**Scheme 12**).^{11,12}

3.1 Preparation of 5-Substituted-1,6-Heptenyne

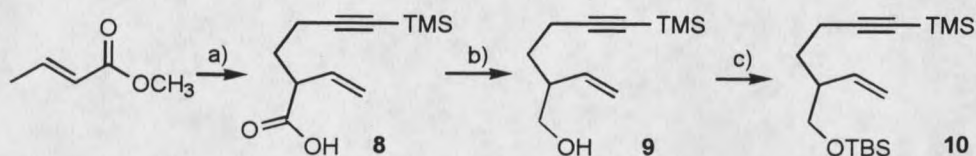
The first substrate targeted for study was 5-hydroxymethyl-1-trimethylsilyl-hept-7-en-1-yne **9** (**Scheme 13**). The analogous 5-hydroxy substrate showed excellent stereoselectivity in zirconocene mediated cyclizations (*vide supra*, section 2.2) and the stereochemistry of the product should be readily determined by NOE spectroscopy. Furthermore, the potential products derived from the 5-hydroxymethyl bearing substrate would closely resemble the prostaglandin skeleton. Early work by Katzenellenbogen prompted us to explore selective deconjugative α -alkylation of the dianion derived from crotonic acid.⁴² Unfortunately, this methodology is most successful with activated electrophiles (e.g. allylic and benzylic). The homopropargylic electrophiles **4** and **4b** are prone to elimination, further exacerbating the problem. Simple nonactivated electrophiles less prone to eliminate, such as butyl bromide, alkylated in moderate yield to provided the α -alkylated deconjugated acid. However, with competing elimination and γ -alkylation reactions, at best the desired product **8** was obtained inconsistently in exceedingly poor yield (< 10%) (**Scheme 14**). Of course, various solvents and

solvents and solvent mixtures (THF, Et₂O, 1,2-DME), bases (LDA, lithium diethylamine, KHMDS), and additives (HMPA, triethanolamineborate)⁴³ were tried and found to be ineffectual.



Scheme 13

Alkylation of methyl crotonate derived enolates proved somewhat more fortuitous. The best results afforded the desired *deconjugated* α -alkylation product ester **8** in 8% yield, which was reduced (LiAlH₄) to provide the desired substrate **9** (which was also protected as its TBS ether **10**) (Scheme 14). Although this procedure provided analytical quantities of the desired product, it offered no entry into a useable supply of material for serious study. The zirconocene cyclization studies concerning this compound are therefore incomplete.



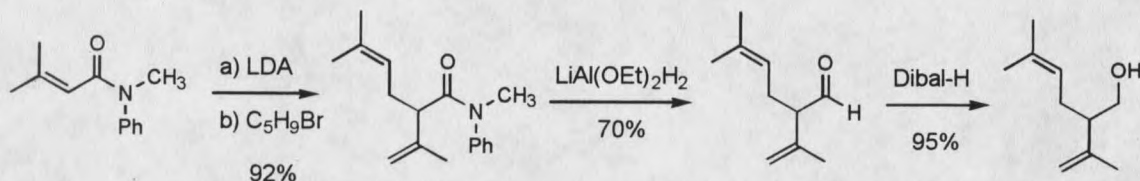
Reagents: (a) i. LDA; ii **4b**; (b) LAH; (c) TBDMSCl-imidazole

Scheme 14

Another avenue towards the desired enyne **10** was envisaged by alkylation of a crotonic acid derived Weinreb amide, because of the proven utility of *alkylation* of acetic acid Weinreb amides.⁴⁴ The crotonic acid Weinreb amide was deprotonated (LDA/THF, -78 °C) and treated with allylbromide as a model electrophile. However, no products derived from alkylation were observed, nor was any starting material recovered. This result was consistent with the observation that Weinreb amides bearing alpha substituents can undergo a unwelcomed retro-ene reaction after enolization.⁴⁵ Although possible, this mode of reactivity does not appear to happen with acetic acid Weinreb amides.

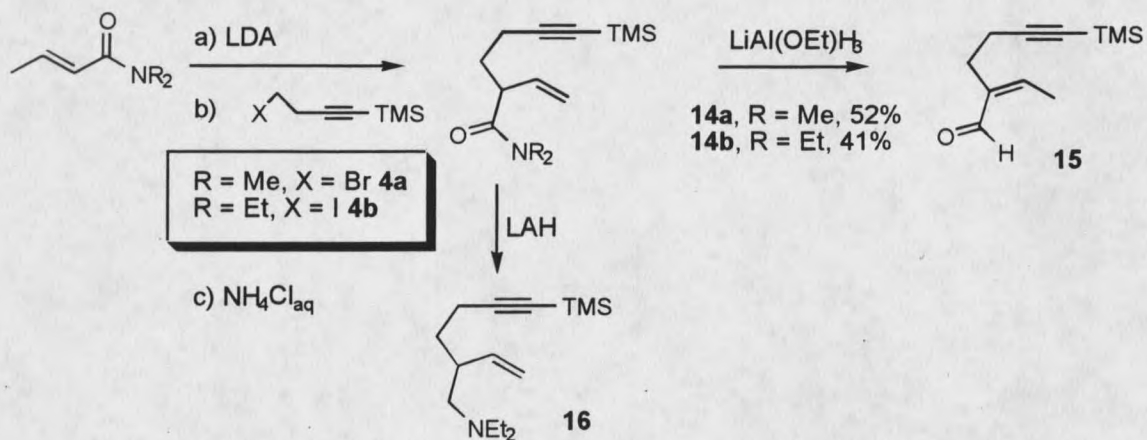
The deconjugative alkylation of crotonic acid tertiary amides was next examined. The alkylation of 3-alkyl (cyclic or acyclic) substituted crotonamides has been exploited by Sniekus for natural product synthesis (**Scheme 15**).⁴⁶ Although the successful conversion of amides to alcohols usually requires harsh reaction conditions,⁴⁷ Brown's $\text{LiAl}(\text{OEt})_2\text{H}_2$ reagent appeared to be an excellent candidate for a mild reduction of the deconjugated amides.^{46,48} Alkylation of *N*-methyl aniline crotonamide was initially investigated because these tertiary amides generally

reduce directly to the alcohol with LiAlH_4 . Unfortunately, alkylation of *N*-methyl aniline crotonamide with either bromo- or iodohomopropargylic electrophiles **4a** or **4b** was unsuccessful.



Scheme 15

Fortunately, the deconjugative alkylation of dialkyl tertiary crotonamides under identical conditions gratifyingly afforded the desired α -alkylated *deconjugated* amides **14a** and **14b** as the sole products, albeit in low (30-50%) yield (**Scheme 16**). For reproducible yields the choice of which electrophilic halide employed was found to be critical. The dimethyl and diethyl amide enolates required 1-iodo-4-trimethylsilyl-3-butyne **4a** and 1-bromo-4-trimethylsilyl-3-butyne **4b**, respectively, for appreciable product formation. It is interesting to note that two closely related amide enolates could have markedly different reactivities.

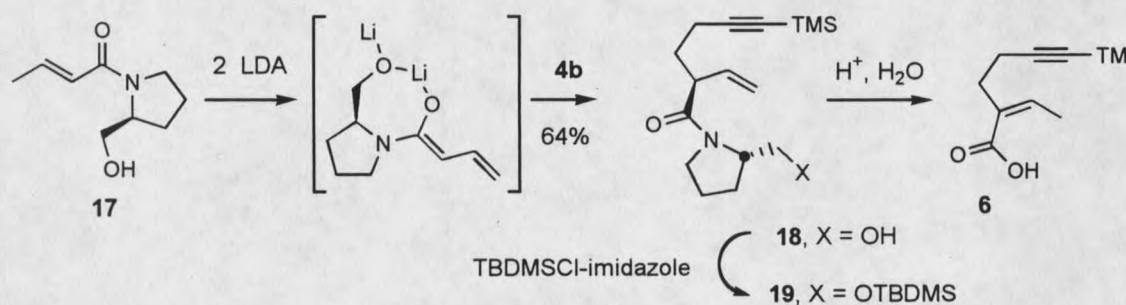


Scheme 16

With enynes **14a** and **14b** in hand, their reduction to the corresponding alcohols was examined. Surprisingly amides **14a,b** were found to be completely impervious to Brown's $\text{LiAl(OEt)}_2\text{H}_2$ reducing reagent. Eventually it was discovered that treating the tertiary amides at $-10\text{ }^\circ\text{C}$ with the monoethoxy complex LiAl(OEt)H_3 effectively reduced the amide to the reconjugated aldehyde **15** (Scheme 16). Apparently, the stabilizing influence of a 3-alkyl substituent (c.f., Scheme 15) is required to prevent reconjugation.⁴⁹ A variety of mild work-ups, such as inverse quenching into buffered solutions followed by *immediate* reduction to the alcohol, offered no improvement. However, this new reduction procedure represents a potentially valuable and mild method for the reduction of tertiary amides. Other reagents proven to be effective for converting tertiary amides to alcohols were investigated, including the ate complex derived from diisobutyl

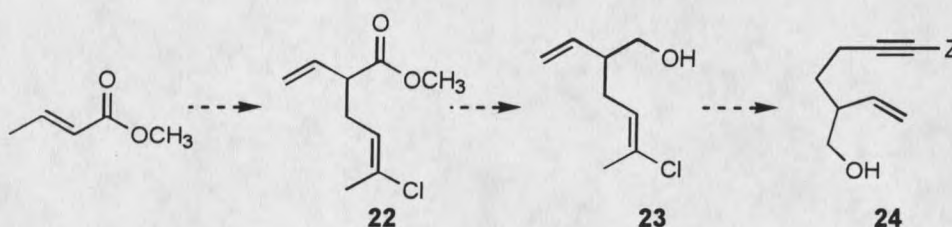
aluminum hydride⁵⁰ (Dibal-H) and *n*-butyllithium; lithium triethylborohydride⁵¹ (Super-Hydride[®]) and borane-lithium pyrrolidide.⁵²

Because β -hydroxy amides are readily hydrolyzable, Evans' prolinol based chiral auxiliary was examined for these alkylations.^{53,54} Although Evans had not demonstrated the utility of deconjugative alkylations, the Evans' chiral amide proved to be a remarkably effective alkylating agent (**Scheme 17**). The desired enyne **18** was procured in 64% isolated yield. The absolute stereochemical assignment of **18** is based on literature precedent.⁵³ Unfortunately, hydrolysis conditions for this β -hydroxy amide proved too harsh and resulted in reconjugation.



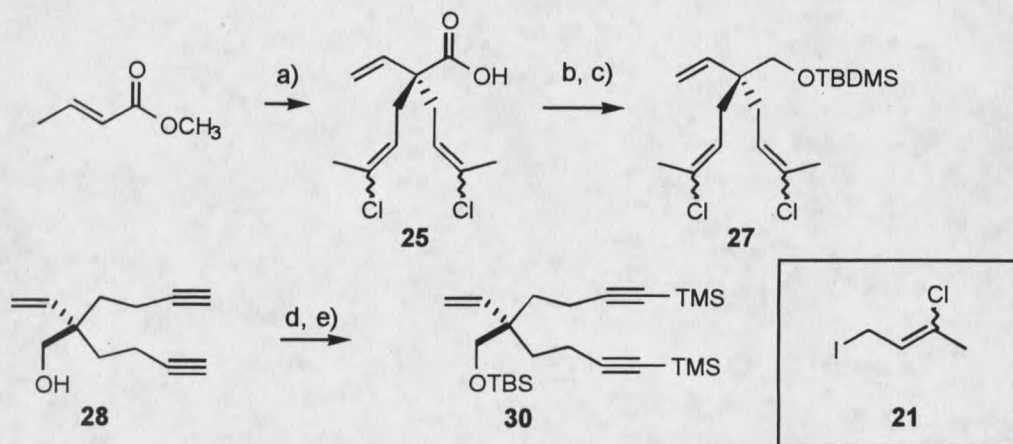
Scheme 17

The last attempt for an efficient synthesis of enyne **9** utilized a 4-bromobut-1-yne equivalent, as depicted in **Scheme 18**. It was anticipated that the activated electrophile 1-iodo-3-chloro-2-butene **21** should be a superior electrophile, without suffering from problematical elimination. The conversion to the terminal acetylene should proceed according to literature precedent.⁵⁵



Scheme 18

The commercially available 1-chloro-3-chloro-2-butene was converted quantitatively (NaI, acetone) into the light sensitive 1-iodo-3-chloro-2-butene **21** immediately before use. This allylic iodide was added to the enolate of methyl crotonate (LDA, $-78\text{ }^{\circ}\text{C}$) and provided the unexpected *dialkylation* product **25** in 88% unoptimized yield (Scheme 19). While experiments were undertaken to favor the monoalkylation product, triene **25** was converted to endiynes **30** as a test substrate. Triene **25** was reduced to the alcohol (LiAlH₄), silylated and treated with potassium 3-aminopropanamide to afford the endiynes **28**. Even though the silylether **27** was desilylated by the harsh conditions employed for the elimination, yields of endiynes **30** were found to improve dramatically when the silylated triene **27** was employed (83%, both steps). Endiynes **28** was subsequently converted to the bis-silylated enyne **30** [1. (a) *n*-BuLi; (b) TMSCl; (c) HCl_{aq}; 2. TBDMSCl-imidazole (92% overall)]. This endiynes was subjected to zirconium(II) mediated cyclization conditions, afforded a plethora of unidentified products. Attempts to maximize formation of the monoalkylation product **22** were unsuccessful.



Reagents: (a) i. LDA; ii. **21**; (b) i. LAH; (c) i. TBDMSCl-imidazole; ii. $\text{KHN}(\text{CH}_2)_3\text{NH}_2$ (83%); (d) i. 2.1 eq *n*-BuLi; ii. 2.2 eq TMSCl iii. 10% HCl_{aq} , 6 hr (95%); (e) TBDMSCl-imidazole (97%).

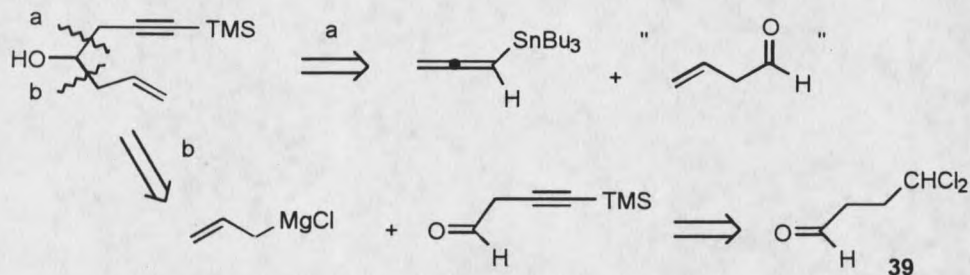
Scheme 19

Fortunately, the three novel amido enynes **14a,b** and **19** and the amine **16** were shown to be extraordinary substrates for zirconocene mediated enyne cyclization (*vide infra*, section 3.3).

3.2 Preparation of 4-Substituted-1,6-Heptenyne

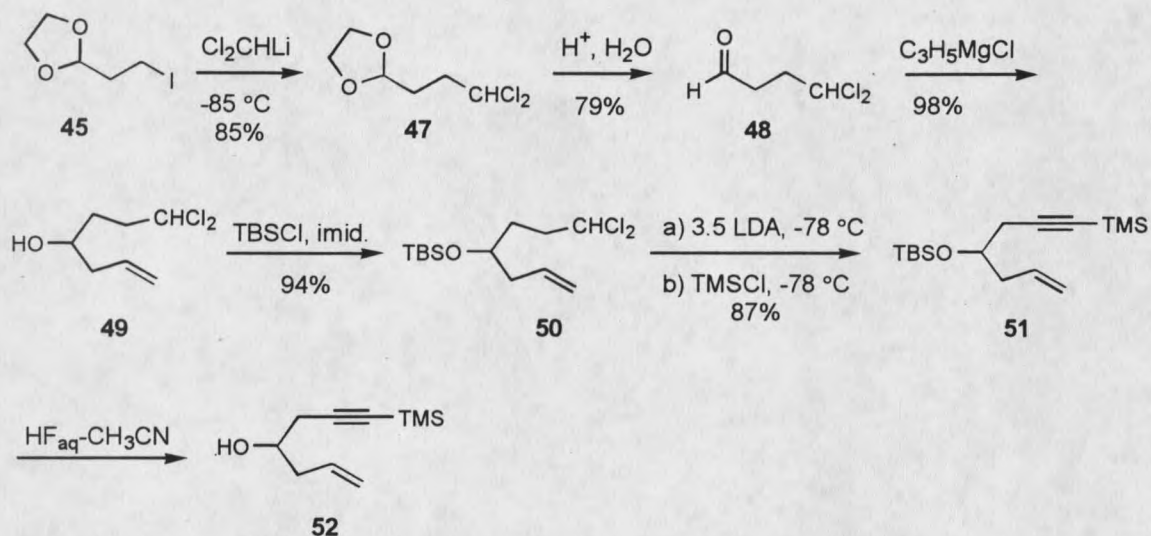
With a variety of 5-substituted-1,6-heptenyne in hand, the preparation of a series of 4-substituted-1-trimethylsilyl hept-6-en-1-yne afforded the next challenges. Retrosynthetic analysis of the desired enynes indicated that rupture of bond *a* would require the use of an allenic nucleophile and an unknown aldehyde. Cleavage of bond *b* would greatly simplify the nucleophilic component but would necessitate the use of an extremely unstable aldehyde. The solution was to use a

novel 4-trimethylsilyl but-3-yn-1-al equivalent (**Scheme 20**) based on the Normant acetylene synthesis,⁵⁶ and proceed via path *b*.



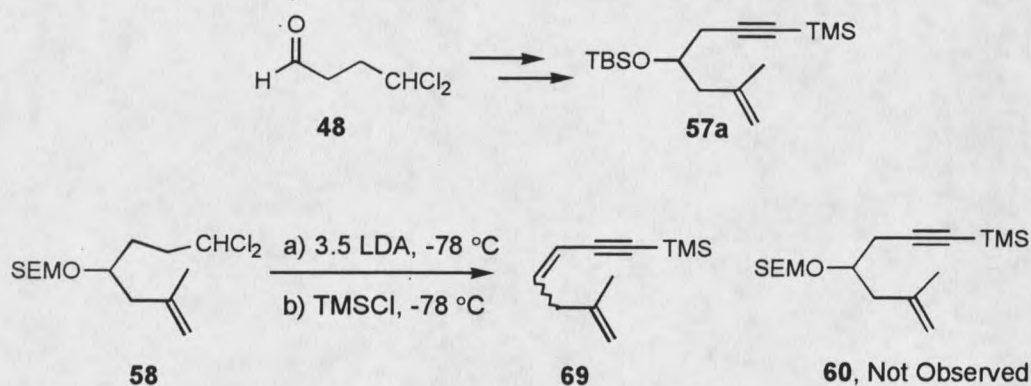
Scheme 20

The aldehyde surrogate, 4,4-dichlorobutanal **48**, was prepared in 67% overall yield by the addition of dichloromethyl lithium to bromo- or 2-(2'-iodoethyl)-1,3-dioxolane **45** at -85 °C, followed by hydrolysis of the dioxolane moiety (2:1 acetone:10% HCl_{aq}) (**Scheme 21**). Addition of allyl magnesium chloride to the aldehyde was uneventful and furnished the key intermediate **49** in 98% yield. *O*-silylation (TBSCl-imidazole) and conversion of the geminal dichloride **50** into terminal acetylene **51** required slow *portion-wise* addition of LDA (3.5 eq) at -78 °C followed by electrophilic capture with TMSCl⁵⁷ at -78 °C. This protocol provided the 1,6-enynes **51** and **52** after *O*-desilylation (HF_{aq}-CH₃CN).



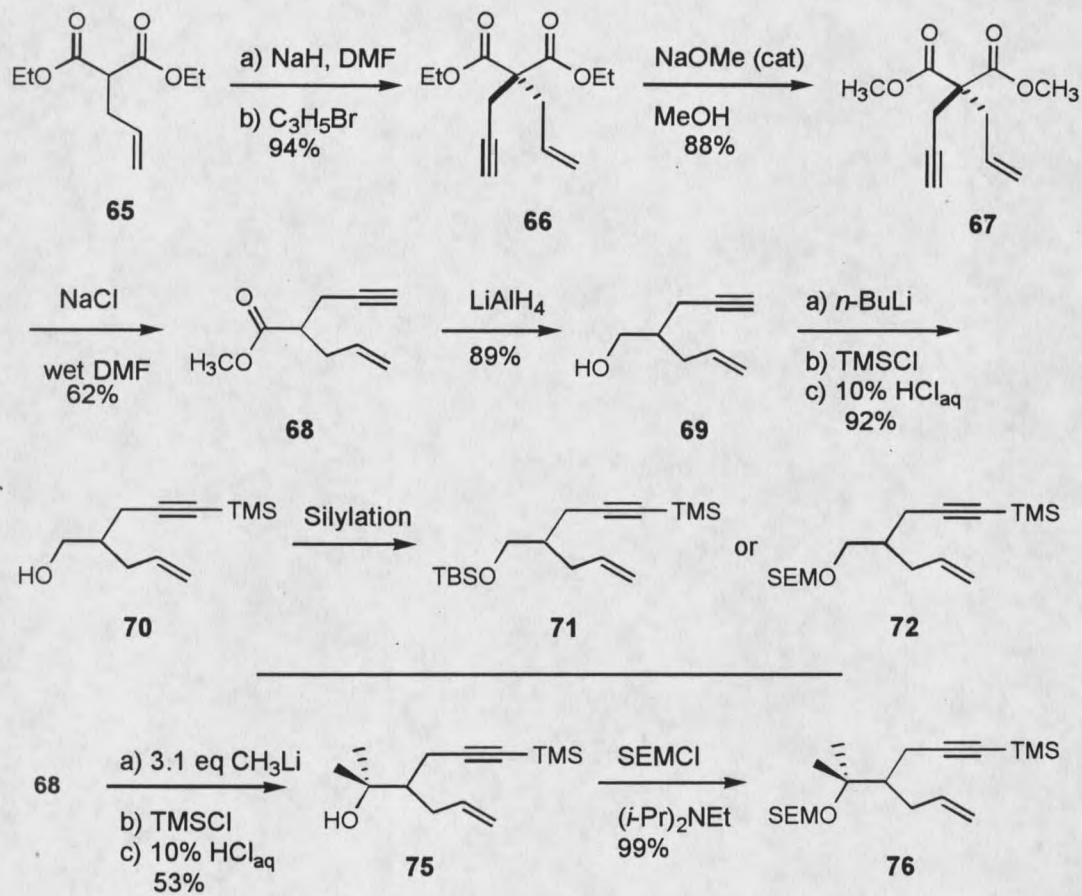
Scheme 21

A series of 4-substituted-6-methyl-1-trimethylsilyl hept-6-en-1-ynes was then prepared in a manner analogous to that used to prepare **51**, except aldehyde **48** was treated with methylmagnesium bromide (**Scheme 22**). A SEM ether proved to be a much better leaving group than a TBS ether, and the only isolated material from the LDA mediated elimination was the bis-elimination product **69**. With an authentic sample of **69** in hand, it was found by G.C. analysis that **69** was present in the elimination reaction undertaken to form **57a**, although only as a minor component.



Scheme 22

The next targets were 4-hydroxymethyl-1-trimethylsilyl hept-6-en-1-yne and various derivatives. Alkylation of commercially available diethyl allyl malonate with propargyl bromide, *trans*-esterification to the methyl ester and decarboxylation (NaCl, wet DMF)⁵⁸ afforded key intermediate **68** (Scheme 23). The 4-(hydroxymethyl)-1-hepten-6-yne derivatives **71**, **72** and **76** were prepared by reduction [1. LiAlH₄; 2. (a) *n*-BuLi; (b) Me₃SiCl; (c) HCl_{aq}] and silylation [TBDMSCl-imidazole, DMF (48% overall for **71** or SEMCl/(*i*-Pr)₂NEt (37% overall for **72**)], or an exhaustive *methylation*/SEM ether formation protocol for **76** [1. (a) CH₃Li; (b) Me₃SiCl; (c) HCl_{aq}; 2. SEMCl/(*i*-Pr)₂NEt (34% overall)].



Scheme 23

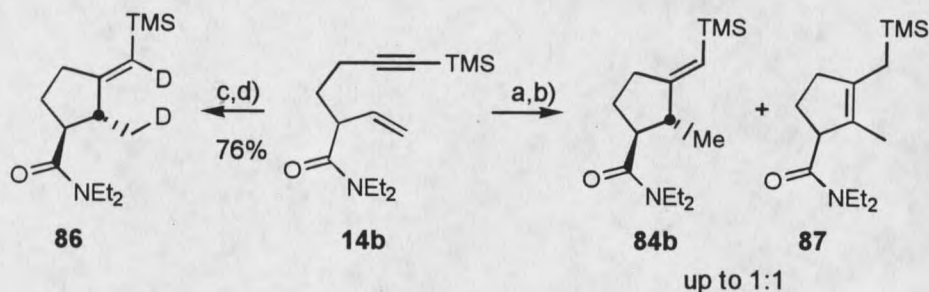
3.3 $\text{Cp}_2(\text{Zr})$ Mediated Enyne Cyclizations

With a variety of new substrates in hand, the focus of attention turned toward the further exploration of discoveries already communicated from these laboratories, specifically to the utilization of $\text{Cp}_2\text{Zr(II)}$ complexes for the annulation of 2,3-disubstituted alkylidenecyclopentane derivatives. Zirconocene mediated

cyclization of enynes bearing carboxamido moieties at the 3-position (e.g., **14a,b** and **19**, counting from the alkene) initially proved problematic (c.f., **Scheme 24**), unlike their previously cyclized hydroxy substituted counterparts **80** and **81** (entries 1 and 2, **Table 4**). Although cyclization could be achieved to some extent using the standard set of reaction conditions, substrate to product conversion was typically below 70% even when 2.1 equiv of $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$ was utilized. [The standard protocol involves treatment of 1 equiv Cp_2ZrCl_2 in THF with $n\text{-BuLi}$ (2 equiv) at $-78\text{ }^\circ\text{C}$ followed by the addition of the appropriate enyne substrate and subsequent stirring ($-78\text{ }^\circ\text{C}$, 0.5 h then $25\text{ }^\circ\text{C}$, 12 h) to generate the corresponding zirconocyclopentene].² In light of the possibility that **14a,b** and **19** might be anomalous with respect to their rate of cyclization, we theorized that competitive decomposition of the active Zr(II) species might be responsible for the observed inefficiency of conversion. It was previously shown that complexation with 4-dimethylaminopyridine (DMAP) conferred enhanced stability on low valent zirconocene complexes.⁵⁹ In accordance with the foregoing hypothesis, cyclization of carboxamides **14a,b** and **19** were performed in the presence of 1 equiv each of $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$ and DMAP. Unfortunately, the yields did not improve. When 2 equiv each of $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$ and DMAP were utilized, the *efficiency of cyclization was gratifyingly restored for the above substrates*, to provide the alkylidenecyclopentanes **84a,b** and **85** in 91%, 93% and 94% isolated yield

respectively. These results constituted the first examples of *carboxamido containing substrates* to successfully undergo zirconium(II) mediated bicyclization. It was possible, that the carboxamido functionality was involved in a previously unobserved Zr-ligation effect, and may have been responsible for observed turpitude of the intended cyclization. In addition, for each of the above cases a very high level of stereoselectivity was observed as a consequence of substrate controlled cyclization. Specifically, the alkylidenecyclopentanes **84a,b** and **85**, the indicated products were formed in greater than 30:1, 99:1 and 50:1 isomeric purity, respectively, as determined by capillary G.C. These results are summarized in **Table 4**. In no cases were any other diastereomers observed.

For carboxamido enynes **14,b** and **19** the use of *strictly alkoxide-free butyllithium* was essential for the successful implementation of this cyclization strategy. Apparently alkoxides catalyze the isomerization of the initial alkylidenecyclopentane to the indicated cyclopentene (**Scheme 24**). A deuterium quench showed no deuterium incorporation α to the carbonyl.



Reagents: (a) 2 eq $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$, 2 eq DMAP with trace *alkoxides*;
 (b) H_2O ; (c) 2 eq $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$, 2 eq DMAP; (d) D_2O

Scheme 24

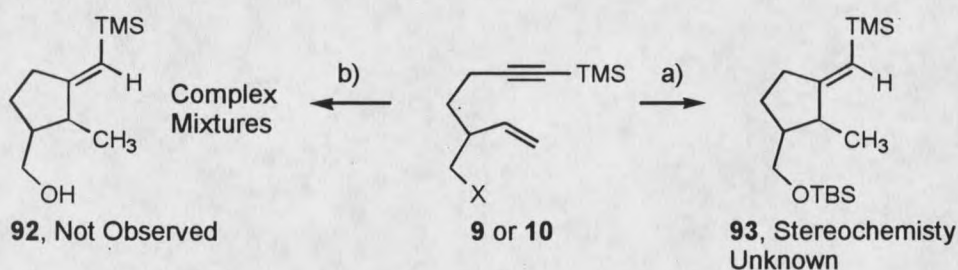
These stereochemical results are more easily understood when considered with the results previously reported from these laboratories for the cyclization of the allylic enynes **80** and **81** bearing a 5-silyloxy or hydroxy substituent (**Table 4**). Under the standard conditions (3 equiv of *n*-BuLi in the case of **80**), led to the formation of the *trans* alkylidenecyclopentanes **90** and **91** in a highly stereocontrolled fashion and in very good yield.¹² In the case of **80** two diastereomeric cyclization products were formed in a 14:1 ratio with the *trans* isomer predominating. For **81**, a single stereochemically homogeneous product **91** was formed as a consequence of $\text{Cp}_2\text{Zr}(\text{II})$ mediated annulation. In the instances of **90** and **91**, evidence for relative stereochemistry derived both from NOE spectroscopy and single-crystal X-ray analysis. The splitting patterns and chemical shift data for the alkylidenecyclopentanes **90** and **91** were closely analogous with one another. Similarly, no observable NOE was detectable between H_a and H_b (although other strong NOE's from the C-2 methyl group to the vinylic methine

were observable). See Table 4 entry 1 for a definition of H_a and H_b. In the case of **91**, the *trans* relationship of the pendant methyl and hydroxy substituents as well as the *E* geometry of the alkyldiene moiety were ultimately confirmed via single-crystal X-ray analysis of the corresponding 4-phenylbenzoate ester.¹² The assignment of relative stereochemistry for **84a,b** and **85** is tentative, as it rests strictly on the *absence* of NOE's between the vicinal hydrogens H_a and H_b and on analogy with the stereochemical outcome of the cyclizations that led to **90** and **91**.

In this connection, the cyclization of amine **31** might be seen as stereochemically informative (**Table 4**). Exposure of **31** to Cp₂Zr(*n*-Bu)₂ under the standard set of experimental conditions (*no DMAP*) provided a predominant diastereomeric alkyldienecyclopentane **95** (stereoselectivity > 40:1) in 88% yield upon protonolysis. As in the previous cases, no detectable NOE was observed between H_a and H_b. However, a strong NOE was observable between H_b and the -CH₂N(Et)₂ methylene. In light of the corpus of data presented above, it is very likely that the stereochemical outcome of the cyclizations **84a,b** and **85** is analogous.

Unlike the 5-hydroxy substituted enyne **81** which cyclized in 81% yield, the diligently sought 5-hydroxymethyl enyne **9** failed to provide any recognizable cyclic products, although the enyne itself was *completely consumed during the course of the reaction* (**Scheme 25**). When converted to the corresponding TBS ether, enyne

7 cyclized in 50% yield under standard conditions as a sole diastereomer based strictly on capillary G.C. analysis. The highly acid-sensitive alkylidenecyclopentane **93** was inseparable from *unreacted* starting material by flash chromatography. Use of an excess of $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$ (with or without the stabilizing influence of DMAP) conferred no better conversion but surprisingly resulted in an increase in side products. This reaction may have been further beleaguered by the necessity of performing the reaction on extremely small scales.

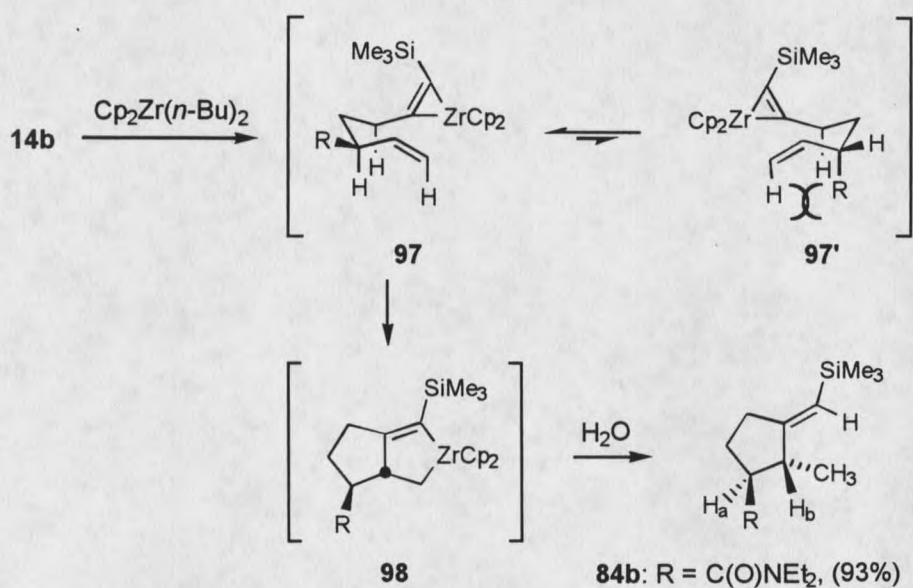


Reagents: (a) (**10**: X = OTBS) i. $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$, $-78\text{ }^\circ\text{C}$ to rt, 12 h; ii. H_2O , 50% conversion. (b) (**9**: X = OH) i. $n\text{-BuLi}$; ii. $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$, $-78\text{ }^\circ\text{C}$ to rt, 12 h; iii. H_2O

Scheme 25

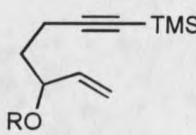
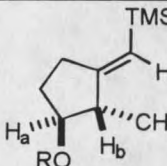
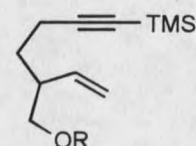
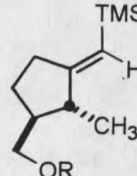
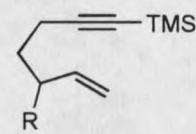
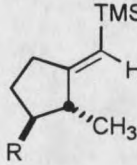
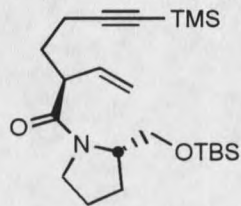
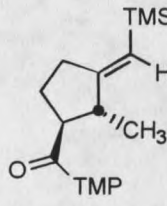
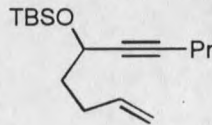
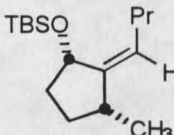
The excellent diastereoselectivity observed for the preceding five cyclizations of can be rationalized as arising from minimization of quasi 1,3-diaxial interactions and 1,3-allylic strain⁶⁰ by the adoption of conformers of the type **97** by the Cp_2Zr -alkyne complex prior to cyclization (**Scheme 26**). According to the following mechanistic interpretation, reductive elimination of butane from $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$ followed by enyne complexation with loss of 1-butene² should generate the transient zirconacyclopropenes **97** for which there are two extreme precyclization

conformers (e.g., **97** and **97'**). Conformers corresponding to **97'** are expected to be disfavored energetically as a consequence of 1,3-allylic strain between the proaxial substituent at C-5 and a methylene hydrogen bound to C-7 and by quasi 1,3-diaxial interactions. Accordingly, cyclization via conformers corresponding to **97**, in which allylic 1,3-strain is minimized, should occur preferentially to provide the exo substituted zirconocyclopentenenes **84b**. A complete summary of these cyclizations appears in **Table 4**.



Scheme 26

Table 4. Preparation of Alkylidene-cyclopentanes by Cyclization of Substituted Enynes with $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$

Entry	Substrate	Product	Yield ^a
1 ^b	 80 , R = TBS		78%
2 ^b	81 , R = H ^d	91	81%
4	 10 , R = TBS		50%
5	9 , R = H ^d	92	0%
6	 14a , R = C(O)NMe ₂		91%
7	14b , R = C(O)NEt ₂	84b	93%
8	31 , R = CH ₂ NEt ₂	95	88%
9	 19		94%
10 ^c			94%

^a Isolated yield. No other diastereomers observed. ^b Ref. 12. ^c Ref. 11. ^d The lithium alkoxide was pre-formed with *n*-BuLi (1.0 eq) before addition of $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$.

The Zr(II) mediated cyclization of several 1-hepten-6-yne substrates bearing a single C-4 substituent were subsequently examined. From the standpoint of substrate derived stereocontrol, substituents of this variety were not expected to be as influential as those proximate to the sites of ring formation. Accordingly, attempted cyclization of the alkoxide **70** failed and resulted in consumption of starting material as with alkoxide **6** (Table 5). Fortunately, cyclization of **71** under the usual conditions (*vide supra*, this section) proceeded without incident to furnish the predominately *trans* alkylidenecyclopentanes **99a** and **99b** (**99a** / **99b** = 2) in 89% yield. The size of the silyloxy protecting group had little effect on the diastereoselectivity, as **73** cyclized with nearly identical diastereoselection (**100a** / **100b** = 2.1). Cyclization of **76** under analogous conditions provided **105a** and **105b** (**105a** / **105b** = 11) in 99% isolated yield. In the case of **99a** and **99b**, the minor isomer **99b** gave a NOE between the C-2 and C-4 hydrogens as would be expected for a molecule possessing *cis* disposed substituents. In addition, the TBDMSOCH₂ ¹H resonance of the *minor* isomer **99b** appeared as multi-line pattern (2 dd, δ 3.40) which could possibly be a consequence of restricted rotation (as might be expected for the *cis* isomer) whereas the TBDMSOCH₂ signal of **99a** appeared as a sharp doublet centered at δ 3.46. For **100a** and **100b**, the *absence* of a NOE between the C-2 and C-4 methines of the major isomer **100a** is consistent

